Morphine and Ketamine Is Superior to Morphine Alone for Out-of-Hospital Trauma Analgesia: A Randomized Controlled Trial

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Study objective: We assess the efficacy of intravenous ketamine compared with intravenous morphine in reducing pain in adults with significant out-of-hospital traumatic pain.

Methods: This study was an out-of-hospital, prospective, randomized, controlled, open-label study. Patients with trauma and a verbal pain score of greater than 5 after 5 mg intravenous morphine were eligible for enrollment. Patients allocated to the ketamine group received a bolus of 10 or 20 mg, followed by 10 mg every 3 minutes thereafter. Patients allocated to the morphine alone group received 5 mg intravenously every 5 minutes until pain free. Pain scores were measured at baseline and at hospital arrival.

Results: A total of 135 patients were enrolled between December 2007 and July 2010. There were no differences between the groups at baseline. After the initial 5-mg dose of intravenous morphine, patients allocated to ketamine received a mean of 40.6 mg (SD 25 mg) of ketamine. Patients allocated to morphine alone received a mean of 14.4 mg (SD 9.4 mg) of morphine. The mean pain score change was −5.6 (95% confidence interval [CI] −6.2 to −5.0) in the ketamine group compared with −3.2 (95% CI −3.7 to −2.7) in the morphine group. The difference in mean pain score change was −2.4 (95% CI −3.2 to −1.6) points. The intravenous morphine group had 9 of 65 (14%; 95% CI 6% to 25%) adverse effects reported (most commonly nausea [6/65; 9%]) compared with 27 of 70 (39%; 95% CI 27% to 51%) in the ketamine group (most commonly disorientation [8/70; 11%]).

Conclusion: Intravenous morphine plus ketamine for out-of-hospital adult trauma patients provides analgesia superior to that of intravenous morphine alone but was associated with an increase in the rate of minor adverse effects. [Ann Emerg Med. 2012;59:497-503.]

Please see page 498 for the Editor’s Capsule Summary of this article.

INTRODUCTION

Background

There is considerable debate about optimal out-of-hospital analgesia for conscious trauma patients and wide variation in practice. Morphine is used commonly; however, there is insufficient evidence about whether this is the optimal analgesic in the out-of-hospital environment. Effectiveness of opioid analgesia for patients with severe trauma may be limited by excessive sedation, respiratory depression, and nausea.

Ketamine is a dissociative agent with analgesic properties and has been used extensively in acute care medicine. Compared with opioids, ketamine has a reportedly low frequency of serious adverse effects in doses used for analgesia and has little effect on the blood pressure and pulse rate. Ketamine is well suited to the out-of-hospital environment. It effectively provides safe analgesia while simultaneously providing anxiolysis and amnesia. A significant benefit of its use is that it has an opioid-sparing effect and improves analgesia in patients with severe pain that is poorly controlled by opioids. What makes ketamine appealing for use in the out-of-hospital setting is that it is purported to allow patients to maintain their pharyngeal reflexes and maintain their own airway, even when fully dissociated.
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Editor’s Capsule Summary

What is already known on this topic
For acutely traumatized patients, out-of-hospital pain control is not promptly and consistently achieved with intravenous opioids.

What question this study addressed
For trauma patients with moderate to severe pain despite an initial dose of morphine 5 mg intravenously, is it more effective to further titrate morphine (5 mg every 5 minutes) or ketamine (10 to 20 mg every 3 minutes)?

What this study adds to our knowledge
In this open-label randomized controlled trial of 135 adults, pain control was superior in the ketamine group by a clinically important margin. Adverse events were minor.

How this is relevant to clinical practice
Supplementing out-of-hospital opioids with low-dose ketamine is an effective strategy to mitigate trauma pain.

Importance
Acute pain is a common presentation to health care clinicians,1,11-13 is often associated with injury,14 and is a significant contributor to disability many months or even years after injury. The effective management of pain is of critical importance in both the short and long term, especially for patients after traumatic injury.

Goals of This Investigation
This study aimed to determine which therapy was most effective in reducing pain intensity before arrival at the hospital, as measured by the verbal numeric pain rating scale. We also examined the incidence of adverse effects and effects of the agents on vital signs.

MATERIALS AND METHODS

Study Design
This study was a prospective, randomized, controlled, open-label, multicenter study to compare the effect of intravenous morphine and ketamine with that of morphine alone in the treatment of moderate (verbal numeric rating score between 5 and 7) to severe (verbal numeric rating score of 8 or greater) traumatic pain before arrival at hospital. The study protocol was approved by Monash University, Victoria, Australia, and the institutional ethics committees at each receiving hospital. The requirement for informed consent was waived in accordance with Australian government regulations. All patients were contacted within 8 weeks to be provided with further information about the study and to gain informed consent to access their medical record. This study was registered with the Australian New Zealand Clinical Trials Registry.

Setting
The study was undertaken in 6 regional and 4 metropolitan sites in Victoria, Australia, between December 2007 and July 2010. The state of Victoria is serviced by a single out-of-hospital provider, Ambulance Victoria, which services 5 rural regions and a metropolitan region. The metropolitan region provides an emergency medical response to Melbourne (population 3.9 million people; area 9,000 km², Jennings et al16). The rural regions provide care to the remainder of the state (population 1.4 million people; area 218,416 km², Jennings et al16). Emergency medical services (EMS) respond to approximately 450,000 calls each year. Ambulance Victoria provides consistent out-of-hospital care across all regions, using clinical practice guidelines that are developed through evidence-based processes approved by a medical advisory committee.

Selection of Participants
Patients were eligible for enrollment if they were assessed by the attending paramedics as having all of the following: were aged 18 years or older, conscious (Glasgow Coma Scale [GCS] score=15), reporting traumatic pain with a verbal numeric rating scale pain score greater than or equal to 5 after a total dose of intravenous morphine of 5 mg (and methoxyflurane according to clinician judgment if clinically indicated), and speaking and able to rate their pain with the verbal numeric rating scale. Patients were excluded if any of the following applied: known allergy to ketamine or morphine, pregnant or lactating, current ischemic chest pain or acute pulmonary edema, severe hypertension (systolic blood pressure >180 mm Hg) and evidence of a head injury, a history of loss of consciousness or GCS score less than 15, inability to obtain venous access, and presumed intoxication with alcohol or illicit substances.

Interventions
Eligible patients were randomized by the attending paramedic through the use of sequentially numbered opaque sealed envelopes containing trial group allocation. Allocation envelopes were block randomized across the 10 trial sites and were distributed to each site in batches of 10. Each batch contained 50% ketamine arm allocations and 50% morphine arm allocations.

After an initial dose of morphine 5 mg intravenously, patients were randomized to receive either intravenous ketamine or intravenous morphine. Morphine 10 mg was diluted in 9 mL of normal saline solution, resulting in 1 mg/mL of solution. Ketamine 200 mg was diluted in 18 mL of normal saline solution, resulting in 10 mg/mL of solution. The dosing schedule for morphine was an initial bolus of up to 5 mg (up to 5 mL), followed by 5-minute increments of 1 to 5 mg (1 to 5
The dosing schedule for ketamine was an initial bolus of 10 or 20 mg (1 or 2 mL), followed by increments of 10 mg (1 mL) every 3 minutes. Paramedics used their clinical judgment on dosing according to patient age and body size. Either morphine or ketamine continued to be administered according to this schedule until the patient became pain free, there was a serious adverse event (eg, profound hypotension, unconsciousness, respiratory depression requiring ventilatory support), or the patient arrived at the receiving emergency department (ED). All 10 participating sites completed identical hardcopy or electronic patient care records and the study case report form for each patient enrolled in the study.

Outcome Measures

The primary outcome was change in the pain verbal numeric rating scale on arrival at the ED. The verbal numeric rating scale measures the patient’s perception of pain intensity with a verbal rating of between 0 and 10 (where 0 represents no pain and 10 represents the worst pain imaginable) and correlates well with the visual analog scale. The verbal numeric rating scale was assessed and recorded by the treating paramedic at baseline (enrollment) and then at 10-minute intervals thereafter until patient handover to the receiving ED. The final verbal numeric rating scale score was assessed and recorded at this time.

The secondary outcomes were change in vital signs and conscious state and the incidence of adverse effects.

Vital signs, including pulse rate, respiratory rate, blood pressure, and conscious state (GCS score) were measured at baseline, at 10-minute intervals thereafter, and at handover to the receiving hospital ED.

Adverse effects were recorded by the treating paramedic on the patient’s record of care and the case report form as free text. Adverse effects of specific interest included excessive sedation, emergence reactions, significant hypotension (systolic blood pressure <90 mm Hg) or hypertension (systolic blood pressure >180 mm Hg), arrhythmias, nausea, and vomiting.

Primary Data Analysis

A reduction of the verbal numeric rating scale pain score of greater than 1.3 was considered clinically significant. The preliminary a priori sample size analysis was based on detecting a mean verbal numeric rating scale difference of 2 points between groups. To achieve a power of 80% and significance level of 5%, enrollment of 110 patients was required in each group to detect a minimum clinically important difference of 1.3 points.

RESULTS

Sufficient numbers of patients should have been enrolled in 10 months. However, enrollment was far slower than anticipated and as low as 2 patients per month. In July 2010, 30 months after commencement of the study, we chose to undertake an unplanned interim analysis of the 136 patients recruited. A biostatistician, blinded to the intervention allocation, undertook the analysis and recommended that the trial should be discontinued, given that a revised sample size calculation based on the actual sample SD (SD = 2.6 points on the verbal numeric rating scale) revealed that a sample of 63 patients was required in each group to detect a minimum clinically important difference of 1.3 points.

Characteristics of Study Subjects

Of the 136 participants with moderate to severe traumatic pain enrolled, 1 withdrew consent to participate in the trial, leaving 135 participants eligible for analysis. Sixty-five participants (48%) had been randomly assigned to the morphine-only group and 70 (52%) to the ketamine group (Figure 1). The baseline characteristics were similar between the 2 groups and are shown in Table 1.

Main Results

Overall, there was a significant difference in mean pain score change between the 2 groups; the ketamine group had a mean verbal numeric rating scale pain change of −5.6 (95% CI −6.2 to −5.0) points out of 10 compared with the morphine group, −3.2 (95% CI −3.7 to −2.7) points (Figure 2). The estimated effect size was −2.4 (95% CI −3.2 to −1.6) points on the 0 to 10 verbal numeric rating scale in favor of ketamine.

Figure 3 illustrates the pain severity reduction by trial group at the 20-minute and final (ED) verbal numeric rating scale assessment.

When the rate of verbal numeric rating scale pain score reduction during the entire patient experience was compared between groups (Figure 4), the ketamine group had a quicker reduction of pain intensity than the morphine-alone group. The median values for these slopes were −3.9 (95% CI −4.4 to −3.1) pain points per minute for the morphine-alone group and −6.5 (−7.2 to −5.4) pain points per minute in the ketamine group. The difference between groups was −2.5 points per minute (95% CI −3.9 to −1.1).

Vital signs were assessed on enrollment and at 10-minute intervals thereafter until arrival at the receiving ED. Changes in vital signs during this time are illustrated in Table 2. There were differences of clinical significance identified between the 2 study groups.

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Paramedics documented any observed or reported adverse effects or adverse events encountered before handover at the ED. An adverse effect was reported for 36 of 135 (27%) patients. The morphine-alone group had 9 of 65 (14%; 95% CI 6% to 25%) adverse effects reported; the ketamine group had 27 of 70 (39%; 95% CI 27% to 51%) adverse effects reported. The nature, frequency, and risk difference of adverse effects reported are described in Table 3. Emergence phenomenon was reported by paramedics in 4 of the ketamine group (6%; 95% CI 2% to 14%), which included symptoms such as dysphoria, agitation, and hallucinations. No patient experienced an adverse event requiring withdrawal from the study.

LIMITATIONS
Methoxyflurane, a fast-acting, inhalational analgesic agent, was administered to most but not all patients enrolled in this study. The administration of methoxyflurane was based on the clinician’s judgment at the time of managing the patient. Methoxyflurane was administered before the paramedic established intravenous access and therefore before randomization and trial allocation. The proportion of patients who received methoxyflurane and the mean dose administered were equivalent between the 2 groups. It is possible that patients who received methoxyflurane achieved better pain reduction than those who did not; however, this was unlikely to favor one study arm over the other.

### Table 1. Demographic data and injury characteristics of patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ketamine Group (n=70)</th>
<th>Morphine-Only Group (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, No. (%)</td>
<td>45 (64)</td>
<td>38 (58)</td>
</tr>
<tr>
<td>Age, y</td>
<td>41 (26–56)</td>
<td>45 (31–66)</td>
</tr>
<tr>
<td>Minimum, maximum</td>
<td>18, 90</td>
<td>18, 96</td>
</tr>
<tr>
<td>Case nature, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremity fracture</td>
<td>26 (37)</td>
<td>29 (45)</td>
</tr>
<tr>
<td>Soft tissue injury</td>
<td>17 (24)</td>
<td>15 (23)</td>
</tr>
<tr>
<td>Fracture, other</td>
<td>14 (20)</td>
<td>13 (20)</td>
</tr>
<tr>
<td>Dislocation</td>
<td>11 (16)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>Burn</td>
<td>2 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Injury Severity Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4 (1–9)</td>
<td>4 (4–4)</td>
</tr>
<tr>
<td>Minimum, maximum</td>
<td>0, 13</td>
<td>0, 22</td>
</tr>
<tr>
<td>Initial pain score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>7.5 (6–9)</td>
<td>7 (6–8)</td>
</tr>
<tr>
<td>Minimum, maximum</td>
<td>5, 10</td>
<td>5, 10</td>
</tr>
<tr>
<td>Number of patients to whom methoxyflurane was</td>
<td></td>
<td></td>
</tr>
<tr>
<td>administered, mL, frequency (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose of methoxyflurane administered, mL</td>
<td>48 (68.6)</td>
<td>40 (61.5)</td>
</tr>
<tr>
<td>Dose of trial drug administered after randomization, mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>35 (20–50)</td>
<td>15 (10–15)</td>
</tr>
<tr>
<td>Minimum, maximum</td>
<td>10, 120</td>
<td>2.5, 60</td>
</tr>
<tr>
<td>Out-of-hospital time, min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>49.5 (34–65)</td>
<td>45 (36–60)</td>
</tr>
<tr>
<td>Minimum, maximum</td>
<td>20, 103</td>
<td>18, 123</td>
</tr>
</tbody>
</table>

IQR, Interquartile range.

Figure 2. Box plots by treatment group of the change in verbal numeric rating scale scores from randomization to ED arrival.
Participants were blinded to the study arm in which they were enrolled, but the clinician was not, a considered decision during the development of the trial for 2 reasons. First, patients receiving ketamine were expected to exhibit obvious and easily identifiable effects (ie, nystagmus, muscle twitching), making the study arm allocation obvious to the clinician and negating the intent of masking. Second, because of the need for both paramedics to double check drugs and doses according to standard operating procedures to ensure patient safety.

Information was not collected about patients potentially eligible for enrollment but not enrolled. It is possible that eligible patients who were not enrolled would have responded differently to their allocated treatment; however, this is unlikely to favor one study arm over the other and unlikely to affect generalizability for patients with predominantly isolated limb injury.

**DISCUSSION**

In this prospective, randomized controlled trial, out-of-hospital use of morphine plus ketamine was superior to that of morphine alone in the reduction of pain intensity in adult patients with moderate to severe pain after trauma. Intravenous ketamine provided safe and effective analgesia to adult patients after injury, conferring an overall pain intensity reduction advantage of 2.4 verbal numeric rating scale points over intravenous morphine alone; patients in the ketamine group had a mean verbal numeric rating scale pain reduction of 5.6 points compared with the morphine group, which had 3.2 points.

The rate of verbal numeric rating scale reduction differed between study groups: the ketamine group had a steeper slope, reflecting a more rapid reduction in pain intensity over time than that of the morphine group. The combination of better efficacy and more rapid effect makes ketamine a desirable addition to out-of-hospital traumatic pain management.

All patients were administered a total of 5 mg of morphine before randomization and enrollment into the study. This was considered an important component of the protocol for 2 reasons. First, in practice, ketamine is not routinely administered as a first-line analgesic. It is generally reserved for patients whose pain proves refractory to morphine.\(^{19,20}\) We believed that administering ketamine as the initial parenteral analgesic agent would not reflect actual practice and be less useful in informing future pain management. Second, ketamine has been shown to act as an adjuvant to morphine,\(^{21}\) and many studies have shown reductions in morphine requirements when ketamine is administered concomitantly.\(^{7,22-24}\) The addition of an N-methyl-D-aspartic acid receptor antagonist such as ketamine is thought to attenuate or prevent the hyperalgesia sometimes induced by opioid administration.\(^{25}\)
Table 3. Frequency of adverse effects observed, by study group.

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Morphone Group (N=65)</th>
<th>Ketamine Group (N=70)</th>
<th>Risk Difference (Morphine-Ketamine Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Risk, %</td>
<td>95% CI</td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>9.2</td>
<td>3.5 to 19.0</td>
</tr>
<tr>
<td>Decreased consciousness (GCS score ≥13)</td>
<td>1</td>
<td>1.5</td>
<td>0.4 to 8.3</td>
</tr>
<tr>
<td>Nystagmus/visual disturbance</td>
<td>1</td>
<td>1.5</td>
<td>0.4 to 8.3</td>
</tr>
<tr>
<td>Decreased systolic blood pressure (&lt;90 mm Hg)</td>
<td>1</td>
<td>1.5</td>
<td>0.4 to 8.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>0 to 5.5</td>
</tr>
<tr>
<td>Increased systolic blood pressure (&gt;180 mm Hg)</td>
<td>0</td>
<td>0</td>
<td>0 to 5.5</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0</td>
<td>0</td>
<td>0 to 5.5</td>
</tr>
<tr>
<td>Tachycardia (&gt;100 beats/min)</td>
<td>0</td>
<td>0</td>
<td>0 to 5.5</td>
</tr>
<tr>
<td>Emergence phenomenon</td>
<td>0</td>
<td>0</td>
<td>0 to 5.5</td>
</tr>
<tr>
<td>Enhanced skeletal tone</td>
<td>0</td>
<td>0</td>
<td>0 to 5.5</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>13.8</td>
<td>6.5 to 24.7</td>
</tr>
</tbody>
</table>

There have been 3 previous studies examining the effectiveness of ketamine on reducing traumatic pain; 2 concluded that ketamine provided safe and effective pain relief,\textsuperscript{26,27} and 1 reported that ketamine reduced the amount of morphine required but was not associated with a reduction in pain intensity.\textsuperscript{23} Galinski et al\textup{23} found that the visual analog scale pain measure (measured in millimeters from 0 to 100, with 0 indicating no pain and 100 indicating worst pain ever) was not statistically different between the morphine and ketamine intervention group and the morphine-alone control group (34.1 versus 39.5 mm; \(P=\text{NS}.\)) At the 30-minute period, a larger proportion of the ketamine group had had their pain reduced to below 30 mm than the morphine group; however, this difference did not reach statistical significance (61% versus 41%; \(P=.20).\textsuperscript{23} Johansson et al\textsuperscript{27}, in their prospective clinical cohort study, used the verbal numeric rating scale and found that the pain scores were significantly different on admission to the hospital: 5.4 (SD 1.9) in the morphine-only group and 3.1 (SD 1.4) in the morphine followed by ketamine group (\(P<.05).\textsuperscript{27}

Clinicians often cite ketamine emergence phenomenon as their reason for avoiding ketamine use as an analgesic in the acute setting. Although this study identified a greater proportion of adverse effects in the ketamine group than the morphine group, they were mild. Emergence phenomenon accounted for 5.7% (4/27) of adverse effects and disorientation accounted for 11.4% (8/72). The incidence of emergence phenomenon is reported to vary from 5% to greater than 30%.\textsuperscript{10,24} The comparatively low incidence of emergence dysphoria encountered in this study is similar to that reported in a large meta-analysis in which doses less than 1 mg/kg were administered to children for ED sedation.\textsuperscript{28} Titrated benzodiazepines quickly and consistently pacify pronounced and unpleasant reactions.\textsuperscript{29} Paramedics had the option of consulting for approval to administer midazolam to counter any such effects; however, despite the reporting of 4 cases of emergence phenomenon, midazolam was not deemed by the attending crew to be necessary. It is possible that the higher reported rate of adverse effects in the ketamine group in general was, at least in part, because the paramedics who were administering the agents were less familiar with ketamine. Given the addition of a new analgesic agent, paramedics were likely to be more cognizant of the known adverse effects (disorientation, emergence phenomenon, tachycardia, hypertension) and therefore more likely to identify and record them compared with recording them for morphine, with which paramedics have considerable experience and comfort. Another study\textsuperscript{23} reported that neuropsychological adverse effects (including hallucinations, dizziness, diplopia, and dysphoria) were significantly greater in the ketamine group. Despite these adverse effects, the authors stated that these effects were weak and brief, none needed treatment, and the patients’ satisfaction between the 2 groups was not different. Other studies have reported no evidence of emergence phenomenon and concluded that ketamine is a safe and effective analgesia.\textsuperscript{26,27} There were no severe adverse events encountered during this study that required withdrawal of the participant from the trial.

There was no clinically significant change of vital signs after enrollment, nor were there any clinically significant differences between study groups. The mean systolic blood pressure of the ketamine group increased slightly, whereas that of the morphine group decreased slightly throughout the duration of care. This slight increase in blood pressure was expected because ketamine causes a centrally mediated catecholamine reuptake inhibition, which generally results in an increase of blood pressure and pulse rate.\textsuperscript{10}

Given the success of intravenous ketamine in the reduction of refractory acute pain, future research should focus on the effectiveness of alternative routes of administration, including intramuscular, intranasal, and topical applications. Furthermore, the utility of various dosing regimens such as continuous or patient-controlled infusion needs to be explored with respect to effectiveness and ease of out-of-hospital maintenance and administration.

Intravenous morphine plus ketamine for out-of-hospital adult trauma patients provides analgesia superior to that of...
intravenous morphine alone. Furthermore, adverse events were uncommon in this nonphysician EMS setting. Further research is recommended to examine alternative routes of administration, optimal dosing, and utility of concomitant opioid administration.

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